INTERVENTIONAL CARDIOLOGY

Steroid-eluting stents in patients with acute coronary syndrome: the Dexamethasone Eluting Stent Italian REgistry

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Objective: To assess immediate and mid-term clinical and angiographic outcomes of the dexamethasone drug-eluting stent (D-DES) in patients with acute coronary syndrome (ACS).

Patients and methods: A prospective, nationwide, controlled, registry. Inflammation plays a key role in ACS, and the anti-inflammatory effects of local elution of dexamethasone in unstable plaques may represent a valid therapeutic approach. All patients had ACS on admission (n = 332). 81.5% of the patients had unstable angina and 18.5% had non-ST elevation myocardial infarction (MI). 47% had ST-T segment changes, 59% had troponin elevation, 77% had elevated C-reactive protein levels and 48% had intermediate–high Thrombolysis in Myocardial Infarction risk score. Patients were treated according to an early invasive approach with 420 D-DES in 387 coronary lesions. Primary end point was the cumulative incidence of death, MI and ischaemia-driven target vessel revascularisation (TVR) at 6 months.

Results: At 30 days, 2 (0.6%) patients died, and sub-acute stent thrombosis occurred in 2 patients. At 6 months, 328 (98.8%) patients were controlled, 3 (0.9%) patients had died, 7 (2.1%) had MI and 28 (8.5%) underwent ischaemia-driven TVR. Therefore, the primary end point occurred in 11.5% of patients. At multivariate analysis, multi-vessel coronary artery disease (odds ratio (OR) = 2.16, 95% CI = 1.47 to 3.17, p = 0.0001) and vessel diameter $\leqslant$ 2.75 mm (OR = 1.64, 95% CI = 1.08 to 2.49, p = 0.02) were independent predictors of 6-month clinical events. Global angiographic restenosis rate was 33.3%.

Conclusion: This is the first large, multicentre analysis of the clinical and angiographic outcomes obtained with D-DES implanted in ACS. D-DES offers a low rate of clinical events at 6 months, but has no anti-restenosis effect.

An "early-invasive approach" for the treatment of patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) is superior to a conservative strategy in patients with either ST-segment depression, troponin elevation or other high-risk indicators. However, recurrence of ischaemia at mid-term in this setting was as high as 22–32.3% in the landmark FRagmin during InStability in Coronary artery disease (FRISC) study and Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction 18 (TACTICS-TIMI) study.[1]

Recently, the high efficacy of drug-eluting stents (DES) in reducing restenosis has been confirmed in a subgroup of patients with NSTE-ACS enrolled in randomised studies not designed, however, to assess the performance of these stents in this specific clinical setting.[2 3]

Dexamet (Abbott Vascular Devices, Galway, Ireland) is a dexamethasone-DES (D-DES) proposed to treat patients with ACS, but data available about its clinical and angiographic results are scarce.

Inflammation plays a predominant role in the cellular mechanisms of unstable plaque. The evolution either towards plaque passivation, healing and stabilisation or towards plaque rupture and the occurrence of major adverse cardiac events (MACE) is influenced by inflammatory mechanisms. Local elution of anti-inflammatory agents is the rationale for the use of D-DES in these patients. This is supported by the previous IMPRESS (Immunosuppressive therapy for the prevention of restenosis after coronary artery stent implantation) studies, in which the systemic administration of high-dose prednisone reduced MACE after percutaneous coronary interventions (PCI).[4]

We assessed the 6-month outcome of patients with NSTE-ACS treated according to an early-invasive strategy by means of PCI with implantation of Dexamet in a nationwide, prospective registry.

METHODS

Between May 2003 and May 2004, 334 patients with NSTE-ACS were enrolled in the registry. MACE were analysed and adjudicated by an independent clinical events committee. Patients entering the Dexamethasone Eluting Stent Italian REgistry (DESIRE) were informed of the study aims, and their consent to participate was obtained.

All patients were treated before angiography with heparin and aspirin. Pre-treatment with ticlopidine or clopidogrel was recommended; thienopyridine was continued for 1 month at least, and aspirin continued indefinitely. Patients were aged >18 years and had NSTE-ACS (either NSTE MI or unstable angina), with single- or multi-vessel coronary disease amenable to PCI performed during the same hospitalisation with at least

Abbreviations: ACS, acute coronary syndrome; BMS, bare metal stents; DES, drug-eluting stent; D-DES, dexamethasone DES; DESIRE, Dexamethasone Eluting Stent Italian REgistry; MACE, major adverse cardiac events; MI, myocardial infarction; NSTE, non-ST-segment elevation; PCI, percutaneous coronary intervention; TVR, target vessel revascularisation

Table 1 Clinical and angiographic results at 6 months

Univariate predictors of the primary end point	MACE rate (%)	OR (95% CI)	p Value
Multi-vessel coronary artery disease	20	2.1 (1.4 to 3.1)	<0.001
Single-vessel coronary artery disease	5.3		
Multi-vessel PCI	24	1.9 (1.4 to 2.7)	<0.001
Single-vessel PCI	7.9		
Complex lesion type (B2/C)	16.7	1.7 (1.2 to 2.4)	<0.003
Simple lesion type (A/B1)	6.6		
Patients with diabetes	20	2.4 (1.2 to 5.0)	<0.01
Patients without diabetes	9.3		
Vessel diameter ⩽2.75 mm	20.1	2.3 (1.1 to 5.3)	<0.03
Vessel diameter >2.75 mm	10		
QCA data*	**Baseline**	**After PCI**	**Follow-up**
Proximal reference diameter (mm)	2.82 (0.54)	3.18 (0.54)	3.04 (0.59)
Distal reference diameter (mm)	2.58 (0.49)	2.53 (0.49)	2.36 (0.56)
MLD (mm)	0.83 (0.4)	2.59 (0.42)	1.64 (0.75)
Diameter stenosis (%)	69.2 (13.6)	10.9 (10.8)	41.2 (23.4)
Late loss in stent (mm)			0.95 (0.64)
Late loss in segment (mm)			0.99 (0.59)

MACE, major adverse cardiac events; MLD, minimum lumen diameter; PCI, percutaneous coronary intervention; QCA, quantitative coronary analysis.
Values given under QCA data are mean (SD).
*Mean (SD) time to angiographic follow-up 195 (45) days.

one D-DES in the culprit lesion. Exclusion criteria were in-stent restenosis, saphenous vein graft or a totally occluded vessel as the culprit lesion; acute ST-segment elevation myocardial infarction (MI); chronic renal failure; vessel diameter <2.5 mm; lesion length >30 mm.

PCI and quantitative coronary analysis

Dexamet is a stainless steel stent coated with phosphorylcholine and loaded with 0.5 μg of dexamethasone/mm^2 of stent surface. The drug is rapidly released from the polymer after stent deployment and completely delivered within 1 week. At least one D-DES had to be implanted in the culprit lesion. Direct stenting was allowed. In patients with multi-vessel disease, non-culprit lesions could be treated with D-DES, bare metal stents (BMS) or balloon angioplasty.

Primary end points were death, MI and ischaemia-driven target vessel revascularisation (TVR) at 6 months.

Secondary end point was binary restenosis at follow-up angiogram (stenosis ⩾50% of the minimal lumen diameter inside the stent or within 5 mm of the stent edges of the lesions treated with D-DES).

RESULTS

At least one Dexamet was implanted in 332 patients; 25.3% of the patients were female, 22% had diabetes, 18.5% had NSTE MI and 23.5% had acute unstable angina, 59% had hypertension and 37.7% had a previous MI. Troponin I was elevated in 59% of patients, and both ST-segment depression and T-wave inversion were observed in 44%. Angiographically, 43% of the patients had multi-vessel coronary artery disease, 49% of the culprit lesions were complex (type B2 or C) and 23% had intraluminal thrombosis.

A total of 358 D-DESs were implanted on 332 coronary culprit stenoses. Additionally, 62 D-DESs were implanted in 55 other (non-culprit) lesions and another 66 non-culprit lesions were treated with 51 BMS or with only balloon dilation in 23 cases. No patient died in hospital, five had MI (one Q-wave MI) and two (0.6%) received blood transfusion due to local vascular bleeding.

End points

Clinical follow-up at 6 months was obtained in 328 (98.8%) patients. The composite of death and MI was observed in 10 (3%) patients. Two (0.6%) had subacute thrombosis; 28 (8.5%) patients underwent ischaemia-driven TVR. The primary end point was therefore reached in 38 of 328 (11.5%) patients. A repeated TVR was also performed in nine additional patients undergoing per-protocol 6-month coronary angiography, although these subjects were asymptomatic and had no signs of ischaemia. Overall, 37 (11.3%) patients underwent repeated TVR.

Table 1 shows the variables associated with the occurrence of the primary end point. Variables associated with the secondary end point were mean (SD) lesion length 14.8 (8.2) vs 10.6 (4.4) mm, p = 0.002, and mean (SD) minimal lumen diameter post-PCI 2.06 (0.5) vs 2.25 (0.5) mm, p = 0.03. Multi-vessel coronary artery disease (OR 2.16, 95% CI 1.47 to 3.17, p = 0.0001) and vessel diameter ⩽2.75 mm (OR 1.64, 95% CI 1.08 to 2.49, p = 0.02) were independent predictors of MACE.

Angiographic results

In all, 6 of the 20 centres that participated in DESIRE performed the angiographic substudy (appendix). Of the 151 patients enrolled in the quantitative coronary analysis substudy, follow-up angiography was obtained in 140 (92.7%) patients, among whom 156 lesions were treated with Dexamet. Binary restenosis was observed in 48 of 140 (34%) patients, or 52 of 156 (33.3%) of lesions. Table 1 shows the quantitative coronary analysis details provided by a core laboratory.

CONCLUSION

DESIRE is the first large clinical experience with D-DES in the specific setting of patients with NSTE-ACS undergoing early-invasive revascularisation with PCI. As such, DESIRE yielded a low rate of subacute thrombosis at 30 days (0.6%) and MACE at 6 months (11.5%). The rapid elution of a potent anti-inflammatory drug such as dexamethasone in patients with ACS might have contributed to the safe and quick stabilisation of the unstable plaque, translating into favourable mid-term clinical results.

The BMS-like angiographic findings reported in this DES study exclude a significant antiproliferative effect of this device, as previously suggested in smaller observations.[5] This may indicate a suboptimal formulation of the drug concentration

and release, with insufficient pharmacological effect in the arterial wall.

The possibility of also obtaining a reduction in neointimal hyperplasia by administering simultaneously high systemic doses of corticosteroids, as shown in the immunosuppressive therapy for the prevention of restenosis after coronary artery stent implantation studies,[4] or associating dexamethasone to other stent-delivered drugs may deserve further investigation.

We remind, however, that the results of DESIRE do not allow a direct comparison with other forms of treatment because of the lack of a control group.

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The Dexamethasone Eluting Stent Italian REgistry (DESIRE) investigators are listed in the appendix.

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APPENDIX

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